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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/506,011	02/17/2000	John Cooper Cox	017227/0155	6856

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EXAMINER

FOLEY, SHANON A

ART UNIT	PAPER NUMBER
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1648

DATE MAILED: 05/25/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/506,011

Applicant(s)

COX ET AL.

Examiner

Shanon Foley

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 December 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-8, 12-17 and 53 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-8, 12-17 and 53 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
- ☒ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

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DETAILED ACTION

In the amendment submitted December 17, 2004, applicant amended claims 1, 8, 12 and 53. Claims 1, 3, 6-8, 12-17 and 53 are pending and under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6-8 and 53 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Upon reconsideration of claims 6-8 and 53, it is determined that the skilled artisan would be unable to make the complex claimed. The claims require that the negatively charged saponin/sterol organic complex be modified to increase the degree of its negative charge and that the positively-charged antigen be modified to increase the degree of its positive charge. These modifications are made to increase the electrostatic association between the organic complex and the antigen, see page 3, lines 13-30 of the disclosure. The working examples discuss different affinities of HpE, HpC, E6E7 antigens, ESO protein and a 6K or 6H polytope with different ISCOMATRIX™. The working examples also discuss increasing the positive charge by mixing the protein of interest at a lower pH or adding 6K or 6H, see examples 8 and 12. However, the scope of the “modifications” to the protein of interest include “adding a further positive charge to the

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antigen...chemical modifications or neutralisation of an antigen's negative charges with positively charged molecules such as arginine", see page 11, lines 14-21.

The skilled artisan would be unable to predict whether such modifications would change the conformation of the antigen or affect antigenicity. Kuo et al. (*Journal of Biochemistry*. 1995; 117 (2): 438-442) teach that antigenicity of cobrotoxin was drastically reduced when some amino acids were modified, while other changes in amino acid sequence had no effect. Kuo et al. also teach that some changes resulted in protein conformational changes as well. See the entire reference. Kuo et al. demonstrate that the skilled artisan would be unable to predict whether a single or multiple residue changes to an antigen would decrease antigenicity and/or the structural conformation. Mateu et al. (*Journal of General Virology*. 1990; 71 (Pt 3): 629-637) discuss binding of monoclonal antibodies to specific conformational epitopes in an antigen. Mateu et al. teach that some residue replacements within an antigen resulted in the disappearance or changes within epitopes. From the teachings of Mateu et al., the skilled artisan would be unable to predict whether the modifications claimed would result in changes of epitopes critical for immune recognition for any given antigen. There are no working examples demonstrating that an antigen modified by the addition of 6K or 6H retains its conformational structure and immunogenicity. There is also no guidance provided for modifying any antigen to increase or establish a positive charge by changing the residue structure while maintaining antigenicity and conformational epitopes. While the electrostatic association between an organic complex and an antigen is a key component to successful adsorption of an antigen to an organic complex, as evidenced by the teachings of Seeber et al, Al-Shakhshir et al. and Callahan et al. (cited previously), a person of skill in the art would be

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unable to predict how to structurally modify any antigen to increase or establish a positive charge while maintaining immunogenicity, see the teachings of Mateu et al. and Kuo et al. above. For these reasons, it is determined that the “modifications” to the antigen encompassed by the claims would require undue experimentation to one skilled in the art.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3 and 12-17 are rejected under 35 U.S.C. 102(a) as being anticipated by Berglindh et al. (WO 98/22135, provided with the IDS submitted 8/25/3), as evidenced by Cox et al. (Vaccine. 1997; 15 (3): 428-256) for reasons of record.

Applicant asserts that since the aggregate of Berglindh et al. does not comprise a sterol-saponin complex that interacts, the reference does not anticipate claim 1.

Applicant's arguments and a review of the reference have been fully considered, but are found to be unpersuasive since the lipid aggregate of Berglindh et al. specifically combines saponins with phosphatidyl inositol, phosphatidyl glycerol, phosphatidic acid and/or lipid A, see claim 1 and page 11, lines 8-13 (emphasis added).

Applicant argues that Berglindh et al. do not suggest any particular arrangement of the saponin and sterol.

Applicant is correct with respect to the exact positioning of the saponin and sterol. However, the instant claims also do not recite a particular arrangement between the

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saponin and the sterol. The claims require an organic complex comprising a saponin and a sterol and the lipid aggregate of Berglindh et al. comprises a saponin and a sterol.

Applicant also states that the skilled artisan would have expected that the presence of saponin would disrupt the tertiary cochleate structure to form an aggregate from the protocol of Berglindh et al.

Applicant's arguments have been fully considered, but are found unpersuasive since this argument contradicts the explicit teachings of Berglindh et al. The reference explicitly states that saponins are combined with sterols in the formulation on page 11, lines 8-13 and claims 1 and 9-12.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1, 3, 12, 13 and 15-17 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Garcon et al. (WO 96/33739).

Claims 1, 3, 12, 13 and 15-17 are drawn to an immunogenic complex comprising a negatively charged organic complex comprising a saponin and a sterol and a positively charged antigen, where the antigen and the organic complex are electrostatically associated. The organic complex further comprises a phosphoglyceride, such as monophosphoryl lipid A.

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Garcon et al. anticipate a vaccine composition comprising an antigen combined with a saponin/sterol complex that induces a CTL response. The liposome structure also contains phosphatidyl choline and/or monophosphoryl lipid A. See page 1, line 18 to page 2, line 20, claims 1-3 and 5-7 and section 1.9.

Although Garcon et al. do not teach electrostatic association between the negatively-charged organic portion and a positively-charged antigen, the reference clearly teaches that the organic complex and the antigen are physically associated with one another, see page 2, lines 29-32, page 5, lines 1-4, page 11, lines 12-22 and pages 12 to 19. Garcon et al. discuss the negative charge and hydrophobicity of the organic complex and that antigens are directly associated with the complex. Since some amino acids are positively charged, these amino acids within the antigen would be naturally attracted to the negatively-charged portion of the organic complex, creating an electrostatic association. In addition, the list of antigens encompassed by the teachings of Garcon et al. are not limited by charge, see page 3, line 1 to page 4, line 32. Therefore, the species of positively-charged antigens is commensurate in scope within the genus of antigens taught by Garcon et al. Therefore, the teachings of Garcon et al. render the invention obvious, if not anticipated.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Garcon et al.

Claim 14 recites specific phosphoglycerides.

Although Garcon et al. do not teach the phosphoglycerides recited, these phosphoglycerides are conventional esters of phosphatidyl choline and would have been obvious alternatives of one another to one of ordinary skill in the art at the time the

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invention was made since Garcon et al. specifically teach that the lipid may be charged to increase the stability of the liposome structure, see page 2, lines 13-15.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 6-8, 12-17 and 53 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 46-55, 63, 64, 67-76 and 85 of copending Application No. 10/622,470. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant application and '470 claims a charged antigen and a negatively charged adjuvant. The adjuvant complexes in both applications consist of identical ingredients. In addition, the instant application claims a genus of antigens treated by the charged composition, which would be obvious over the species claimed in '470.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.


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Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shanon Foley whose telephone number is (571) 272-0898. The examiner can normally be reached on M-Th 6:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Shanon Foley
Primary Examiner
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